EXHIBIT F

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The Dynamics of Drug Absorption, Distribution, and Elimination

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To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Although obviously a function of the amount of drug administered, the concentrations of active, unbound (free) drug attained also depend upon the extent and rate of its absorption, distribution (which mainly reflects relative binding to plasma and tissue proteins), metabolism (biotransformation), and excretion. These disposition factors are depicted in Figure 1–1 and are described in this chapter.

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are, therefore, important. The determining characteristics of a drug are its molecular size and shape, degree of ionization, relative lipid solubility of

Figure 1–1. Schematic representation of the interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its locus of action.

Possible distribution and binding of metabolites are not depicted.

its ionized and nonionized forms, and its binding to tissue proteins.

When a drug permeates a cell, it obviously must traverse the cellular plasma membrane. Other barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells (skin). Despite such structural differences, the diffusion and transport of drugs across these various boundaries have many common characteristics, since drugs in general pass through cells rather than between them. The plasma membrane thus represents the common barrier.
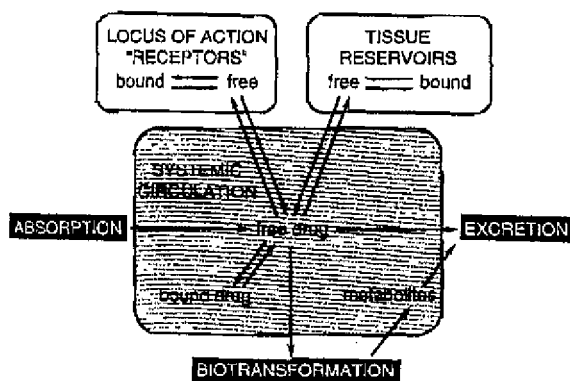
Cell Membranes. The plasma membrane consists of a bilayer of amphipathic lipids, with their hydrocarbon chains oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer vary according to the particular membrane and can move laterally, endowing the membrane with fluidity, flexibility, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as receptors, ion channels, or transporters to elicit electrical or chemical signaling pathways and provide selective targets for drug actions.

Most cell membranes are relatively permeable to water either by diffusion or by flow resulting from hydrostatic or osmotic differences across the membrane, and bulk flow of water can carry with it drug molecules. Such transport is the major mechanism by which drugs pass across most capillary endothelial membranes. However, proteins and drug molecules bound to them are too large and polar for this type of transport to occur; thus, transcapillary movement is limited to unbound drug. Paracellular transport through intercellular gaps is sufficiently large that passage across most capillaries is limited by blood flow and not by other factors (see below). As described later, this type of transport is an important factor in filtration across

glomerular membranes in the kidney. Important exceptions exist in such capillary diffusion, however, since "tight" intercellular junctions are present in specific tissues and paracellular transport in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions (see below). Although bulk flow of water can carry with it small, water-soluble substances, if the molecular mass of these compounds is greater than 100 to 200 daltons, such transport is limited. Accordingly, most large lipophilic drugs must pass through the cell membrane itself by one or more processes.

Passive Membrane Transport. Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In the former, the drug molecule usually penetrates by passive diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane, the lipid:water partition coefficient of the drug, and the cell surface area. The greater the partition coefficient, the higher is the concentration of drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the unbound drug is the same on both sides of the membrane if the drug is a nonelectrolyte. For ionic compounds, the steady-state concentrations will be dependent on differences in pH across the membrane, which may influence the state of ionization of the molecule on each side of the membrane and on the electrochemical gradient for the ion.

Weak Electrolytes and Influence of pH. Most drugs are weak acids or bases that are present in solution as both the nonionized and ionized species. The nonionized molecules are usually lipid-soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility.

Therefore, the transmembrane distribution of a weak electrolyte usually is determined by its pK_a and the pH gradient across the membrane. The pK_a is the pH at which half of the drug (weak electrolyte) is in its ionized form. To illustrate the effect of pH on distribution of drugs, the partitioning of a weak acid ($pK_a = 4.4$) between plasma (pH = 7.4) and gastric juice (pH = 1.4) is depicted in Figure 1–2. It is assumed that the gastric mucosal membrane behaves as a simple lipid barrier that is permeable only to the lipid-soluble, nonionized form of the acid. The ratio of nonionized to ionized drug at each pH is readily calculated from the Henderson–Hasselbalch equation. Thus, in plasma, the ratio of nonionized to ionized drug is 1:1000; in gastric juice, the ratio is 1:0.001. These values are given in brackets in Figure 1–2. The total concentration ratio between the plasma and the gastric juice would therefore be 1000:1 if such a system came to a steady state. For a weak base with a pK_a of 4.4, the ratio would be reversed, as would the thick horizontal arrows in Figure 1–2, which indicate the predominant species at
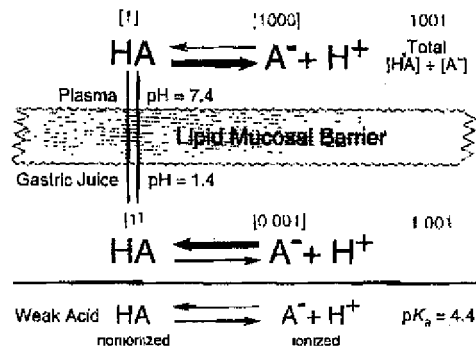

Figure 1–2. Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.

each pH. Accordingly, at steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side—a phenomenon termed *ion trapping*. These considerations have obvious implications for the absorption and excretion of drugs, as discussed more specifically below. The establishment of concentration gradients of weak electrolytes across membranes with a pH gradient is a purely physical process and does not require an active transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient is, however, an active process.

Carrier-Mediated Membrane Transport. While passive diffusion through the bilayer is dominant in the disposition of most drugs, carrier-mediated mechanisms also can play an important role. Active transport is characterized by a requirement for energy, movement against an electrochemical gradient, saturability, selectivity, and competitive inhibition by cotransported compounds. The term *facilitated diffusion* describes a carrier-mediated transport process in which there is no input of energy and therefore enhanced movement of the involved substance is down an electrochemical gradient. Such mechanisms, which may be highly selective for a specific conformational structure of a drug, are involved in the transport of endogenous compounds whose rate of transport by passive diffusion otherwise would be too slow. In other cases, they function as a barrier system to protect cells from potentially toxic substances.

The responsible transporter proteins often are expressed within cell membranes in a domain-specific fashion such that they mediate either drug uptake or efflux, and often such an arrangement facilitates vectorial transport across cells. Thus, in the liver, a number of basolaterally localized transporters with different substrate specificities are involved in the uptake of bile acids and amphipathic organic anions and cations into the hepatocyte, and a similar variety of ATP-dependent transporters in the canalicular membrane export such compounds into the bile. Analogous situations also are present in intestinal and renal tubular membranes. An important efflux transporter present at

these sites and also in the capillary endothelium of brain capillaries is P-glycoprotein, which is encoded by the multidrug resistance-1 (*MDR1*) gene, important in resistance to cancer chemotherapeutic agents (Chapter 52). P-glycoprotein localized in the enterocyte also limits the oral absorption of transported drugs since it exports the compound back into the intestinal tract subsequent to its absorption by passive diffusion.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is concerned primarily with a parameter designated as *bioavailability*, rather than absorption. *Bioavailability* is a term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action. For example, a drug given orally must be absorbed first from the stomach and intestine, but this may be limited by the characteristics of the dosage form and/or the drug's physicochemical properties. In addition, drug then passes through the liver, where metabolism and/or biliary excretion may occur before it reaches the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is large, bioavailability will be substantially reduced (the so-called *first-pass effect*). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (*see* below), and the choice of the route of drug administration must be based on an understanding of these conditions.

Oral (Enteral) *versus* Parenteral Administration. Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 1–1.

Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical. Disadvantages to the oral route include limited absorption of some drugs because of their physical characteristics (*e.g.*, water solubility), emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH,

irregularities in absorption or propulsion in the presence of food or other drugs, and necessity for cooperation on the part of the patient. In addition, drugs in the gastrointestinal tract may be metabolized by the enzymes of the intestinal flora, mucosa, or the liver before they gain access to the general circulation.

The parenteral injection of drugs has certain distinct advantages over oral administration. In some instances, parenteral administration is essential for the drug to be delivered in its active form. Availability is usually more rapid, extensive, and predictable than when a drug is given by mouth. The effective dose therefore can be more accurately delivered. In emergency therapy and when a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be a necessity. The injection of drugs, however, has its disadvantages: asepsis must be maintained; pain may accompany the injection; it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary; and there is the risk of inadvertent administration of a drug when it is not intended. Expense is another consideration.

Oral Ingestion. Absorption from the gastrointestinal tract is governed by factors such as surface area for absorption, blood flow to the site of absorption, the physical state of the drug (solution, suspension, or solid dosage form), its water solubility, and concentration at the site of absorption. For drugs given in solid form, the rate of dissolution may be the limiting factor in their absorption, especially if they have low water solubility. Since most drug absorption from the gastrointestinal tract occurs *via* passive processes, absorption is favored when the drug is in the nonionized and more lipophilic form. Based on the pH-partition concept presented in Figure 1–2, it would be predicted that drugs that are weak acids would be better absorbed from the stomach (pH 1 to 2) than from the upper intestine (pH 3 to 6), and *vice versa* for weak bases. However, the epithelium of the stomach is lined with a thick mucous layer, and its surface area is small; by contrast, the villi of the upper intestine provide an extremely large surface area (~200 m^2). Accordingly, the rate of absorption of a drug from the intestine will be greater than that from the stomach even if the drug is predominantly ionized in the intestine and largely nonionized in the stomach. Thus, any factor that accelerates gastric emptying will be likely to increase the rate of drug absorption, while any factor that delays gastric emptying will probably have the opposite effect, regardless of the characteristics of the drug.

Drugs that are destroyed by gastric juice or that cause gastric irritation sometimes are administered in dosage forms with a coating that prevents dissolution in the acidic gastric contents. However, some enteric-coated

Table 1-1
Some Characteristics of Common Routes of Drug Administration*

ROUTE	ABSORPTION PATTERN	SPECIAL UTILITY	LIMITATION AND PRECAUTIONS
Intravenous	Absorption circumvented Potentially immediate effects	Valuable for emergency use Permits titration of dosage Usually required for high-molecular-weight protein and peptide drugs Suitable for large volumes and for irritating substances, when diluted	Increased risk of adverse effects Must inject solutions *slowly*, as a rule Not suitable for oily solutions or insoluble substances
Subcutaneous	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for some insoluble suspensions and for implantation of solid pellets	Not suitable for large volumes Possible pain or necrosis from irritating substances
Intramuscular	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant medication May interfere with interpretation of certain diagnostic tests (*e.g.,* creatine kinase)
Oral ingestion	Variable; depends upon many factors (*see* text)	Most convenient and economical; usually more safe	Requires patient cooperation Availability potentially erratic and incomplete for drugs that are poorly soluble, slowly absorbed, unstable, or extensively metabolized by the liver and/or gut

*See text for more complete discussion and for other routes.

preparations of a drug also may resist dissolution in the intestine, and very little of the drug may be absorbed.

Controlled-Release Preparations. The rate of absorption of a drug administered as a tablet or other solid oral-dosage form is partly dependent upon its rate of dissolution in the gastrointestinal fluids. This factor is the basis for the so-called *controlled-release, extended-release, sustained-release,* or *prolonged-action* pharmaceutical preparations that are designed to produce slow, uniform absorption of the drug for 8 hours or longer. Potential advantages of such preparations are reduction in the frequency of administration of the drug as compared with conventional dosage forms (possibly with improved compliance by the patient), maintenance of a therapeutic effect overnight, and decreased incidence and/or intensity of undesired effects by elimination of the peaks in drug concentration that often occur after administration of immediate-release dosage forms.

Many controlled-release preparations fulfill these expectations. However, such products have some drawbacks. Generally, interpatient variability, in terms of the systemic concentration of the drug that is achieved, is greater for controlled-release than for immediate-release dosage forms. During repeated drug administration, trough drug concentrations resulting from controlled-release dosage forms may not be different from those observed with immediate-release preparations, although the time interval between trough concentrations is greater for a well-designed controlled-release product. It is possible that the dosage form may fail, and "dose-dumping" with resultant toxicity can occur, since the total dose of drug ingested at one time may be several times the amount contained in the conventional preparation. Controlled-release dosage forms are most appropriate for drugs with short half-lives (less than 4 hours). So-called controlled-release dosage forms are sometimes developed for drugs with long half-lives (greater than 12 hours). These usually more expensive products should not be prescribed unless specific advantages have been demonstrated.

Sublingual Administration. Absorption from the oral mucosa has special significance for certain drugs, despite the fact that the surface area available is small. For example, nitroglycerin is effective when retained sublingually because it is nonionic and has a very high lipid solubility. Thus, the drug is absorbed

very rapidly. Nitroglycerin also is very potent; relatively few molecules need to be absorbed to produce the therapeutic effect. Since venous drainage from the mouth is to the superior vena cava, the drug also is protected from rapid hepatic first-pass metabolism, which is sufficient to prevent the appearance of any active nitroglycerin in the systemic circulation if the sublingual tablet is swallowed.

Rectal Administration. The rectal route often is useful when oral ingestion is precluded because the patient is unconscious or when vomiting is present—a situation particularly relevant to young children. Approximately 50% of the drug that is absorbed from the rectum will bypass the liver; the potential for hepatic first-pass metabolism is thus less than that for an oral dose. However, rectal absorption often is irregular and incomplete, and many drugs cause irritation of the rectal mucosa.

Parenteral Injection. The major routes of parenteral administration are intravenous, subcutaneous, and intramuscular. Absorption from subcutaneous and intramuscular sites occurs by simple diffusion along the gradient from drug depot to plasma. The rate is limited by the area of the absorbing capillary membranes and by the solubility of the substance in the interstitial fluid. Relatively large aqueous channels in the endothelial membrane account for the indiscriminate diffusion of molecules regardless of their lipid solubility. Larger molecules, such as proteins, slowly gain access to the circulation by way of lymphatic channels.

Drugs administered into the systemic circulation by any route, excluding the intraarterial route, are subject to possible first-pass elimination in the lung prior to distribution to the rest of the body. The lungs serve as a temporary storage site for a number of agents, especially drugs that are weak bases and are predominantly nonionized at the blood pH, apparently by their partition into lipid. The lungs also serve as a filter for particulate matter that may be given intravenously, and, of course, they provide a route of elimination for volatile substances.

Intravenous. Factors relevant to absorption are circumvented by intravenous injection of drugs in aqueous solution, because bioavailability is complete and rapid. Also, drug delivery is controlled and achieved with an accuracy and immediacy not possible by any other procedure. In some instances, as in the induction of surgical anesthesia, the dose of a drug is not predetermined but is adjusted to the response of the patient. Also, certain irritating solutions can be given only in this manner, since the blood vessel walls are relatively insensitive, and the drug, if injected slowly, is greatly diluted by the blood.

As there are advantages to the use of this route of administration, so are there liabilities. Unfavorable reactions are likely to occur, since high concentrations of drug may be attained rapidly in both plasma and tissues.

Because of this, it is advisable to intravenously administer a drug slowly by infusion rather than by rapid injection, and with close monitoring of the patient's response. Furthermore, once the drug is injected there is no retreat. Repeated intravenous injections are dependent upon the ability to maintain a patent vein. Drugs in an oily vehicle or those that precipitate blood constituents or hemolyze erythrocytes should not be given by this route.

Subcutaneous. Injection of a drug into a subcutaneous site often is used. It can be used only for drugs that are not irritating to tissue; otherwise, severe pain, necrosis, and tissue sloughing may occur. The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a sustained effect. Moreover, it may be varied intentionally. For example, the rate of absorption of a suspension of insoluble insulin is slow compared with that of a soluble preparation of the hormone. The incorporation of a vasoconstrictor agent in a solution of a drug to be injected subcutaneously also retards absorption. Absorption of drugs implanted under the skin in a solid pellet form occurs slowly over a period of weeks or months; some hormones are effectively administered in this manner.

Intramuscular. Drugs in aqueous solution are absorbed quite rapidly after intramuscular injection, depending upon the rate of blood flow to the injection site. This may be modulated to some extent by local heating, massage, or exercise. For example, jogging may cause a precipitous drop in blood sugar when insulin is injected into the thigh, rather than into the arm or abdominal wall, since running markedly increases blood flow to the leg. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus. This has been attributed to the different distribution of subcutaneous fat in males and females, since fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular or subcutaneous injection. Very slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository vehicles. Antibiotics often are administered in this manner. Substances too irritating to be injected subcutaneously sometimes may be given intramuscularly.

Intraarterial. Occasionally a drug is injected directly into an artery to localize its effect in a particular tissue or organ—for example, in the treatment of liver tumors and head/neck cancers. Diagnostic agents are sometimes administered by this route. Intraarterial injection requires great care and should be reserved